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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/985,873	11/06/2001	Tione Buranda	7201102	4518

52297 7590 01/25/2008
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EXAMINER	
LAM, ANN Y	

ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
01/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	09/985,873	BURANDA ET AL.
	Examiner	**Art Unit**
	Ann Y. Lam	1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-68 and 74-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-68 and 74-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 102 / 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 54-59, 62-68 and 74-77 are rejected under 35 U.S.C. 102(e) as anticipated by Nelson et al. 6,074,827 or, in the alternative, under 35 U.S.C. 103(a) as obvious over Nelson et al. 6,074,827, in view of Felder et al., 6,232,066

As to claim 54, Nelson et al. teach a microfluidic device having an enrichment channel. A variety of different enrichment media may be present in the enrichment channel (col. 5, lines 28-29) and one class of enrichment media or materials are

chromatographic media or materials, particularly sorptive phase materials, such as affinity chromatographic materials in which a binding member is covalently bound to an insoluble matrix, where the binding member may be for example an antibody, antigen or olignucleotide, and where the insoluble matrix to which the binding member is bound may be particles such as porous glass or polymeric beads (col. 5, line 66 – col. 6, line14.) Nelson et al. also teach that it may be necessary to employ a retention means to keep the chromatographic material in the enrichment channel, and that glass frits or plugs of agarose gel may be employed to cover the fluid outlets or inlets of the chamber, where the frits or plugs allow for fluid flow but not for particle or other insoluble matrix flow out of the enrichment channel (col. 6, lines 14-22.) Typically, as the sample flows through the enrichment channel, the analyte comprising fraction will be retained in the enrichment channel by the chromatographic material and the remaining waste portion of the sample will flow out of the channel through the waste outlet (col. 6, lines 25-29.) Nelson et al. also give an example of polymeric beads coated with antibodies or other target-specific affinity binding moiety (col. 6, lines 30- 43.) Thus, Nelson et al. disclose biomolecules bound to beads.

Nelson et al. also teach that the enrichment channel may be present in a variety of configurations. The length of the channel may be for example 1 microns to 5 millimeters, and the cross-sectional dimension may be 1 microns to 200 microns, and the cross-sectional shape of the channel may be circular, ellipsoid, rectangular, trapezoidal, square, or other convenient configuration (col. 5, lines 17-27.)

Nelson et al. also teach an embodiment having a serial array of affinity zones (244, 246, 248, 250), each affinity zone being provided with an enrichment medium that has a specific affinity for a selected component of the fraction of interest (col. 17, lines 27-31 and fig. 16), for example the affinity zones may have immobilized oligonucleotide probes having a sequence complementary to a sequence in a target DNA in a mixture of DNA fragments of different lengths and base compositions (col. 17, lines 35-42.) (That is, each affinity zone has a different immobilized oligonucleotide for capturing different DNA fragments.) As the eluted fraction passes serially through the affinity zones (244, 246, 268, 250), any target DNA present in the fraction that is complementary to the probe in one of the affinity zones will become bound in that affinity zone (col. 17, lines 42-45.) The affinity zones are provided with detectors (243, 245, 247, 249) configured to detect and optionally to quantify a signal (such as fluorescence) from components of interest bound in the affinity zones (col. 17, lines 45-49.) Nelson et al. teach that as the skilled artisan will appreciate, any form of biomolecular recognition may be employed as a capture principle in the affinity zones, such as receptor-ligand binding, antibody-antigen interactions, etc. and thus the disclosed methods and devices can be useful for carrying out immunoassays, receptor binding assays, and the like, as well as for nucleic acid hybridization assays (col. 17, lines 49-65.)

The serial array of affinity zones, including the portion of the channel in between each affinity zone, in figure 16 is deemed to be a column, since it has the structural elements of a column. While the affinity zones of the enrichment channel of figure 16

are wider than the channel portions in between the affinity zones, the affinity zones and the channels in between are deemed to form a column because they form a structure with a linear axis and is elongated and Applicants only recite a column in general. It is also noted that the channel of the microfluidic device of Nelson et al. is considered a column even if it is in the micro-scale especially since Applicants also disclose in the specification that the present invention encompasses microcolumns of microfluidic devices (see for example the description of figures 7a and 7b.) The oligonucleotides bound to for example beads as disclosed by Nelson et al. in one affinity zone are deemed to be a first type of biomolecules, and the beads in that affinity zone are deemed to comprise a first population of beads immobilized within a first region of the column. The oligonucleotides bound to beads in the next affinity zone are deemed to be a second type of biomolecules, and the beads in that affinity zone are deemed to comprise a second population of beads immobilized in a second region in the column.

Moreover, Nelson et al. recite in claim 1 combining a first binding member of an affinity binding pair with a nucleic acid portion of a nucleic acid mixture to form a bound entity (i.e., complex) comprising a nucleic acid and a labeled first binding member, and contacting in the enrichment region the bound entity (i.e., complex) with the second binding member of the affinity binding pair which is bound to a solid support (e.g., bead). Because Nelson et al. teach that the serial affinity zones are provided with detectors (243, 245, 247, 249) configured to detect and optionally to quantify a signal (such as fluorescence) from components of interest bound in the affinity zones (col. 17, lines 45-49), it is understood that the fluorescence in each channel is the fluorescence

from different types of labels, or tags, on the different molecules in each affinity zone as each affinity zone requires a different detector for detecting different fluorescence.

Alternatively, it is not clear whether each affinity zone has a different type of fluorescent label. However, Felder et al. teach that molecules on a bead may be labeled, directly or indirectly, with different labels such as fluorescent labels (tags) so that the beads and molecules can be identified and distinguished from each other using the appropriate detection method, e.g., fluorescence detection technique (col. 8, lines 40-61.) Felder et al. also teach that the target can be labeled, for example by a fluorescent label (col. 25, lines 50- 63) and the target can be detected by any of a variety of procedures (col. 26, lines 64-66) including fluorescence detection of energy transfer from one label to another label (col. 27, lines 19-26.) It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize different fluorescent labels as taught by Felder et al. in the Nelson et al. invention because Felder et al. teach that using different fluorescent labels provide the benefit of distinguishing between different beads with different molecules.

Also, Applicant has amended to the claims to include the limitations that the first and second population of beads each have beads of having known surface occupancy (interpreted to mean number of molecules, as is understood from a reading of the specification). It is first noted that this limitation appears to relate to intended use. That is, determining the number of molecules on each bead is a step limitation and the number of molecules are capable of being determined by the skilled artisan, for example by the same means which allows for determining concentration of the analytes

as disclosed by Felder et al., or by other means which are also disclosed by Applicant). A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, as is the case here as discussed above, then it meets the claim.

It is noted that in any event, Felder et al. disclose that the molecules on the beads are known--see col. 7, lines 42-58, disclosing that the number of anchors in a test region can be of a specific number, i.e., known (see col. 13, lines 23-62, disclosing synthesis of the anchors, specifically that oligonucleotide anchors are dissolved at a concentration routinely determined empirically and a specific volume of it is distributed onto the substrate, or alternatively the anchors can be synthesized directly on the surface; an see col. 26, lines 31-58, disclosing that the presence of control linkers permits calibration of the number of functional (e.g. able to interact with linkers) anchors within and between test regions (i.e. tests the capacity of each locus of the array to bind target, for purposes of normalizing signals), serves as a basis for quantitation of the amount of bound target, aids in localization of the anchor loci and/or provides a positive control e.g. in cases in which there is no signal as a result of absence of target in a sample.) It is noted that in the modification of the Nelson et al. invention, which discloses enrichment and/or quantification of the analytes (col. 17, lines 45-49), the skilled artisan would be suggested by the Felder et al. disclosure to utilize such specific

means (i.e., of using known number of labeled molecules) to quantify the analytes which is only generally disclosed by Nelson et al.

As to claim 55, Nelson et al. teach that as the eluted fraction passes serially through the affinity zones (244, 246, 268, 250), any target DNA present in the fraction that is complementary to the probe in one of the affinity zones will become bound in that affinity zone (col. 17, lines 42-45.)

As to claims 56 and 65, Applicants claim that the second population is layered over the first population of beads. The populations of beads in the affinity zones are deemed to be layered one over the other, as they are situated adjacent each other although with an obstructive feature in between the populations. It is noted that the populations can be considered to be layered one over the other even where there is an obstructive features--see Applicants' claim 66 which depends from claim 65. It is also noted that the limitation "layering" is interpreted as a product-by-product limitation and, thus the prior art meets the limitation since it discloses the same product as explained above.

Alternatively, while Nelson et al. teach separate, sequential zones for the different population of beads, given the teachings of Felder et al. that beads with different molecules can be distinguished from each other using different fluorescent labels, layering population of beads one over the other is within the skills of the ordinary artisan as it allows for the same detection and appears to provide the same function as a design choice wherein the populations of beads are placed in separate zones having an obstructive feature separating the populations of beads. It is also noted that layering

one over the other is interpreted to encompass layering one adjacent to another horizontally as this appears to be the case in Applicants' disclosure, which also discloses a microfluidic device.

As to claims 57 and 66, figure 16 of the Nelson et al. patent disclose an obstructive feature separating the populations of beads in the different affinity zones (244, 246, 248, 250).

As to claims 58, 59, Felder et al. teach that the target can be detected by any of a variety of procedures (col. 26, lines 64-66) including fluorescence detection of energy transfer from one label to another label (col. 27, lines 19-26.) In such a detection technique, the labels have a pre-complexing fluorescent signature, and a post-complexing signature that after the energy transfer that is different from the pre-complexing fluorescent signature.

As to claim 62, Nelson et al. give an example of polymeric beads coated with antibodies or other target-specific affinity binding moiety (col. 6, lines 30- 43.) Nelson et al. also teach that the affinity zones may have immobilized oligonucleotide probes having a sequence complementary to a sequence in a target DNA in a mixture of DNA fragments of different lengths and base compositions (col. 17, lines 35-42.)

As to claim 63, figure 16 of Nelson et al. show a plurality of microfluidic channels (e.g. 236, 238, and the channels including 244, 246, 248, 250), wherein at least one of the channel (i.e., the channel including 244, 246, 248 and 250) comprises a first and second population of beads and biomolecule and tags as recited by Applicants.

As to claim 64, the two channels as recited by Applicants are deemed to be the channel including (244) and (246), and the channel including (248) and (250).

As to claim 67, the device comprises a single entry port (i.e., the port or opening from sample reservoir 233) for analyte delivery. It is noted that the claim does not say, the device has *only* one entry port.

As to claim 68, there are multiple entry ports for analyte delivery (i.e., ports or openings from reservoir 231 and 233, both of which are capable of delivering analyte), wherein each entry port correlates to a single microfluidic channel (the ports each open to a different microfluidic channel in fig. 16.)

As to claims 74-77, neither Nelson et al. nor Felder et al. teach that each bead contains 10 million binding sites or has greater than 2 million receptors. However, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. (MPEP 2144.05 IIA, citing *In re Aller*, 105 USPQ 233). In this case, the cited references disclose the general conditions of the claims and the number of bindings sites or number of receptors recited by Applicant falls within a workable range, i.e., as would be desirable for detecting a particular concentration of analytes, by using the appropriately sized beads and number of receptors, and thus discovery of such workable ranges involves only routine skill in the art. It is also noted that while the term "receptors" is not recited in the independent claim, it is understood that "receptors" refers to receptors on the biomolecules on the beads.

Claim 60 is rejected under 35 U.S.C. 102(e) as anticipated by Nelson et al. 6,074,827, in light of Aylott et al., 6,331,438, or, in the alternative, under 35 U.S.C. 103(a) as obvious over Nelson et al. 6,074,827, in view of Felder et al., 6,232,066, and in light of Aylott et al., 6,331,438.

As to claim 60, Applicants further recite that the pre-complexing fluorescent signature and post-complexing fluorescent signatures are lifetime measurements. Felder et al. teach that the target can be detected by any of a variety of procedures, including time-resolved fluorescence (col. 27, lines 24-25), which is the same as lifetime measurements, as evidenced by Aylott et al. (see col. 8, lines 17-20.)

Claim 61 is rejected under 35 U.S.C. 102(e) as anticipated by Nelson et al. 6,074,827, in view of Bronstein et al., 6,243,980, or, in the alternative, under 35 U.S.C. 103(a) as obvious over Nelson et al. 6,074,827, in view of Felder et al., 6,232,066, and further in view of Bronstein et al., 6,243,980.

Nelson et al. (or alternatively Nelson et al. in view of Felder et al.) disclose the invention substantially as claimed (see above), except for the first biomolecule comprising the claimed amino acid sequence (also known in the art as FLAG).

However Bronstein et al. teach that this amino acid sequence (FLAG) is a member of a binding pair and is used to bind to its member to attach to a solid phase for

washing and reaction with other reagents (col. 7, lines 7-20, and claims 1 and 11). It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize FLAG as taught by Bronstein et al. in the Nelson et al. device because Bronstein et al. teach that this amino acid sequence provides the benefit attaching a complex to a solid phase for washing and reaction processes. The skilled artisan would have reasonable expectation of success in using FLAG and its binding partner as taught by Bronstein et al. using the Nelson et al. device because Nelson et al. teach that any form of biomolecular recognition may be employed as a capture principle in the affinity zones, such as receptor-ligand binding, antibody-antigen interactions, etc. and thus the disclosed methods and devices can be useful for carrying out immunoassays, receptor binding assays, and the like, as well as for nucleic acid hybridization assays (col. 17, lines 49-65.)

Response to Arguments

Applicant's arguments filed October 4, 2007 have been fully considered but they are not persuasive.

Applicant argues that the newly amended claims now recite that the beads having known surface occupancy, which are not disclosed by Nelson et al., and that Nelson et al. generally teach enrichment and thus there is no need to provide known surface chemistry, and that the only example teaching quantification relates to an embodment wherein the analyte is labeled, rather than the molecules on the beads. The

argument is not persuasive because, as indicated in the grounds of rejection above, the limitations regarding known surface occupancy relate to intended use. That is, determining the number of molecules on each bead is a step limitation and the number of molecules are capable of being determined by the skilled artisan, for example by the same means which allows for determining concentration of the analytes as disclosed by Felder et al., or by other means which are also disclosed by Applicant). A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, as is the case here as discussed above, then it meets the claim. It is also noted in the grounds for rejection that, in any event, known surface occupancy is also disclosed by Felder et al., which disclose that the molecules on the beads are known--see col. 7, lines 42-58, disclosing that the number of anchors in a test region can be of a specific number, i.e., known (see col. 13, lines 23-62, disclosing synthesis of the anchors, specifically that oligonucleotide anchors are dissolved at a concentration routinely determined empirically and a specific volume of it is distributed onto the substrate, or alternatively the anchors can be synthesized directly on the surface; an see col. 26, lines 31-58, disclosing that the presence of control linkers permits calibration of the number of functional (e.g. able to interact with linkers) anchors within and between test regions (i.e. tests the capacity of each locus of the array to bind target, for purposes of normalizing signals), serves as a basis for quantitation of the amount of bound target, aids in localization of the anchor loci and/or provides a positive

control e.g. in cases in which there is no signal as a result of absence of target in a sample.) In the modification of the Nelson et al. invention, which discloses enrichment and/or quantification of the analytes (col. 17, lines 45-49), the skilled artisan would be suggested by the Felder et al. disclosure to utilize such specific means (i.e., of using known number of labeled molecules) to quantify the analytes which is only generally disclosed by Nelson et al. In regards to Applicant's argument that the only embodiment in Nelson et al. that relates to quantification of analytes discloses that the analytes are labeled, rather than the molecules on the beads being labeled. This is not persuasive as the skilled artisan, in modifying the Nelson et al. invention, to label the molecules on the beads as suggested by Felder et al. for quantification, among other purposes disclosed, would understand that the other disclosures regarding how quantification is carried out (e.g., by using known number of anchors) would also apply in such modification to quantitate the analytes.

Applicant also argue that the Office did not assert that Felder et al. teach different populations of beads with different labels, but that in any case, the claims have been amended to recite that the first and second type of biomolecules are not found in the same population of beads. Examiner notes however that the different population of beads, with different biomolecules, are disclosed by Nelson et al. as discussed above (i.e., the Felder et al. reference is not relied upon for teaching this limitation), and that in the modification of the Nelson et al. invention by the teachings of Felder et al. to provide different labels on the biomolecules the substrate to detect different analytes, the skilled artisan would recognize that such different labels suggested by Felder et al. would be

provided in the appropriate different populations of beads, i.e., different labels on the different types of molecules, each of which are provided in different populations as disclosed by the Nelson et al.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on Mon.-Fri. 10-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ann Y. Lam
Primary Patent Examiner